

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/020737

International filing date (day/month/year)
29.06.2004

Priority date (day/month/year)
02.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D413/10, C07D413/14, C07D263/20, A61K31/422, A61P31/04

Applicant
MERCK & CO., INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2004/020737

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-17

because:

☒ the said international application, or the said claims Nos. 15-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-17 (in part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/020737

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-17
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III-1. The claims are i. a. directed to "prodrugs" of structurally defined compounds. Since in the absence of any further definition it is unclear which compounds are covered by this in terms of structures, no opinion can be given on this part of the claims. The search as well as the examination with respect to prodrugs is limited to prodrugs as defined on page 10 of the description.

III-2. Claims 15-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the art

The following documents have been cited:

- D1: WO 02/059116 A (BARBACHYN MICHAEL R ; GORDEEV MIKHAIL F (US); UPJOHN CO (US); GAGE JAM) 1 August 2002 (2002-08-01)
- D2: EP-A-0 352 781 (DU PONT) 31 January 1990 (1990-01-31)
- D3: US-A-5 565 571 (BARBACHYN MICHAEL R ET AL) 15 October 1996 (1996-10-15)
- D4: WO 02/051819 A (REDDY RESEARCH FOUNDATION) 4 July 2002 (2002-07-04)
- D5: WO 03/048136 A (KYORIN PHARMACEUTICALS CO LTD ; FUKUDA YASUMUCHI (JP); MERCK & CO INC) 12 June 2003 (2003-06-12)
- D6: WO 03/027083 A (KYORIN SEIYAKU KK ; FUKUDA YASUMICHI (JP); MERCK & CO INC (US); HAMMON) 3 April 2003 (2003-04-03)
- D7: US-A-5 627 181 (RIEDL BERND ET AL) 6 May 1997 (1997-05-06)

D8: US 2002/161029 A1 (HLASTA DENNIS J ET AL) 31 October 2002 (2002-10-31)
D9: WO 01/58885 A (HESTER JACKSON B JR ; UPJOHN CO (US)) 16 August 2001
(2001-08-16)
D10: US-A-5 523 403 (BARBACHYN MICHAEL R) 4 June 1996 (1996-06-04)

V-2. Novelty (Art. 33(2) PCT)

The present claims differ from the compounds disclosed in D1-D4 mainly in that a substituent R1a is required on the cyclopropyl ring which is not disclosed in D1-D4. The claims differ from D5 and D6 in the addition of a second aryl moiety. The claims differ from D7-D10 (see compounds indicated in the search report) mainly in that in these documents the cyclopropyl moiety is attached to the second aryl ring via a methylene, carbonyl or amino spacer.

The claims fulfil thus Art. 33(2) PCT

V-3. Inventive step (Art. 33(3) PCT)

D1-D10 all deal with oxazolidine antibiotics. Closest prior art for present claim 1 is seen in D1 which discloses also compounds in which an oxazolidine ring and a cyclopropyl moiety are linked by two aryl/heteroaryl rings. The difference lies in the substituent R1a which cannot be H in the present claims and in the proviso in claim 1 which disclaims compounds in which the cyclopropyl moiety is attached to a N atom of the second heterocyclic rings. The problem to be solved is the provision of further oxazolidine antibiotics.

D5/D6 disclose the claimed cyclopropyl- and azabicyclohexane substituents defined as X in the present claims. D2-D4 disclose compounds in which the cyclopropyl moiety is attached to carbon atoms of the second aryl rings (see passages cited in the search report). D7-D10 disclose compounds that differ from the claims only in that the cyclopropyl moiety is attached to the second aryl ring via a small spacer. All features of the claimed compounds are known from D1-D10 for oxazolidine antibiotics. The skilled

man would have needed no inventive skills to arrive at the presently claimed solution of the above problem taking the combined teaching of e. g. D1-D4 on the one hand and D5/D6 on the other hand.

The claims do not fulfil Art. 33(3) PCT).

Re Item VIII

Certain observations on the international application

The proviso in claim 1 is unclear (Art. 6 PCT). Apparently it intends to exclude the compounds of D1, however, the compounds of D1 lack the R1a substituent and are thus not covered by the claims.

The definition of Ar/Hetar as "heterocycle, heterocyclyl or heterocyclic" in claim 1 is considered obscure (Art. 6 PCT) since the difference between these definitions it is not clear.